# Chapter 1. Introduction

## 1.0. Impact of ETS on the Health of Californians – Update to the OEHHA 1997 Report

OEHHA has, in this document, updated the report on health effects of environmental tobacco smoke first released in 1997 (Cal/EPA, 1997) and later published by the U.S. National Cancer Institute (NCI, 1999). This report has been prepared under the Toxic Air Contaminant process and is being used in the deliberations by the state's Scientific Review Panel on Toxic Air Contaminants and the Air Resources Board on the identification of Environmental Tobacco Smoke as a Toxic Air Contaminant. The Children's Environmental Health Protection Act (SB 25, statutes of 1999; Health and Safety Code Section 29669.5) requires OEHHA to evaluate exposure patterns and special susceptibility of infants and children when conducting a health effects assessment under the Toxic Air Contaminant program. We review a number of health endpoints relevant to infants and children in this document, including SIDS, asthma, low birth weight, pre-term delivery, and childhood cancers.

Disease risks due to inhalation of tobacco smoke are not limited to smokers, but extend to nonsmokers who inhale environmental tobacco smoke (ETS) at home or work, or in public places. Authoritative reviews over the past two decades have presented scientific evidence linking ETS exposures to a number of adverse health outcomes. *Smoking and Health: A Report of the Surgeon General* (U.S. DHEW, 1979) noted several adverse respiratory outcomes in children and adults, as well as some acute cardiovascular effects associated with involuntary exposure to tobacco smoke. The 1982 *A Report of the Surgeon General* (U.S. DHHS, 1982), which focused on the carcinogenic effects of active smoking, raised the concern that involuntary smoking may cause lung cancer. The large series of epidemiological investigations following the publication of that report provided compelling evidence of a causal relationship and subsequently the 1986 *Report of the Surgeon General* (U.S. DHHS, 1986), as well as reviews by the National Research Council (NRC, 1986) and the U.S. Environmental Protection Agency (U.S. EPA, 1992), concluded that ETS exposure causes lung cancer. The NRC (1986) and U.S. EPA (1992) also found ETS exposure to be associated with lower respiratory tract illnesses in young children, as well as with other adverse respiratory outcomes.

Many people are exposed to ETS. Table 1.2 presents estimates of impacts for some of the health effects associated with ETS exposure, and predictions of the numbers of people potentially affected in California, mainly based on extrapolations from national estimates. Recent state and local restrictions on smoking at work and in public places in California, in addition to the California Department of Health Services' (CDHS) advertisement campaign by the Tobacco Control Program, have significantly reduced ETS exposures of nonsmokers in California. The predictions in Table 1.2 estimate the number of Californians adversely impacted by ETS utilizing the most recent data from the California Adult Tobacco Surveys (CDHS, 2001). Exposure to ETS remains a significant public health concern in California.

Evidence on ETS-related effects has expanded considerably since the major comprehensive reviews contained in the *Reports of the Surgeon General* and published by U.S. EPA and NRC. The State of California therefore undertook a broad review of ETS, covering the major health endpoints potentially associated with ETS exposure that was published as an NCI monograph in 1999. This update reviews the literature published since the original report to the SRP and NCI monograph. We summarize the findings of the original report on each endpoint, and add to those findings based on our review of the more recent literature.

### 1.1. Organization of the Report

The update begins with introductory material on the methodology of the update. In Part A, prepared by the Air Resources Board (originally Chapter 2 in Cal/EPA 1997) an updated overview is presented on measurements of ETS exposure, particularly as they relate to characterizations of exposure in epidemiological investigations, and on prevalence of ETS exposure found in studies conducted in California and nationally. Chapters 3 through 5 address the developmental and reproductive effects of ETS exposure. Perinatal manifestations of developmental toxicity are addressed in Chapter 3, postnatal manifestations in Chapter 4, and male and female reproductive effects in Chapter 5. In Chapter 6, acute and chronic respiratory health effects are described, including some that, under standard definitions (see *e.g.*, U.S. EPA, 1991; CDHS, 1991), are considered to be developmental effects, such as pulmonary development and childhood asthma induction. Chapter 7 describes the evidence for carcinogenic effects of ETS exposure beginning with a discussion of all sites combined for children and

adults. The chapter then describes the evidence for specific sites: lung, nasal sinus, cervical and bladder cancer (sites for which active smoking has been causally linked to cancer induction), and breast, stomach, brain, leukemia, lymphomas, non-Hodgkin's lymphomas and other rare childhood cancers (sites for which previous reviews have determined there was equivocal or suggestive evidence for an etiologic role for active smoking). Chapter 8 updates the review of the evidence for the impact of ETS exposure on coronary heart disease.

### 1.2. Definition of ETS

ETS is also called "second-hand smoke", and ETS exposure is frequently described interchangeably as "involuntary smoking" or "passive smoking." ETS is formed from the smoldering of a cigarette or other tobacco product, and from smoke exhaled by the smoker (NRC, 1986). There are other minor contributors such as the smoke that escapes while the smoker inhales, and some vapor-phase components that diffuse into the environment. Once released into the environment of the smoker, components are diluted by the ambient air, diffusing in and being transported through it. These smoke constituents may also aggregate with other components in the air, and further age and change in character. This complex mixture is defined as ETS, and inhalation of it, as ETS exposure. In some ways this may be an overly restrictive definition when it comes to assessing effects from prenatal smoke exposures. Because the fetus cannot actively smoke, all of its exposure to tobacco smoke constituents is "passive" or "involuntary". Although exposure of the fetus due to maternal smoking during pregnancy is not considered to be ETS exposure in this report, recent studies examining effects related to fetal exposure are reviewed as they are helpful in understanding biologic plausibility, potential additive effects of prenatal and postnatal exposures (for example in SIDS), and in hypothesis generation. In a similar vein, active smoking is reviewed briefly for some of the other endpoints including reproductive toxicity, and cancer.

Except where otherwise specified, the effects of ETS exposure included in this report are for non-smokers. The definition of non-smoker is somewhat study-dependent and ranges from never smoked at all to never regularly smoked more than 100 cigarettes in the subject's lifetime, and in one study non-smoker is defined as not smoking in the previous two weeks. For the endpoints associated with pregnancy, LBW and PTD, and for cardiac death, breast cancer

incidence, and lung cancer death, the target populations are nonsmokers. In general ex-smokers are not excluded. Estimates for the childhood endpoints, asthma, otitis media and SIDS, include only never-smokers.

### 1.3. Methodology

This update and the original review are based on exhaustive searches of the literature, including electronic searches (*e.g.*, Medline, Toxline), and formal requests for information ("data call-in") by ARB through mailed notices and a *California Regulatory Notice Register* announcement. While published, peer-reviewed literature serves as the primary source of data, additional sources, for example from abstracts of meeting presentations or doctoral dissertations, may be included, particularly if they provide information in an area where data are lacking.

Methodological issues that were considered in the review of the epidemiologic literature in the original report and this update include: 1) the sample size of the study, which affects the power to detect an effect; 2) the extent to which the analysis or design takes into account potential confounders, or other risk factors; 3) selection bias, or whether the study groups were comparable; and 4) the potential for bias in ascertaining exposure. These factors were considered when identifying those studies of highest quality.

An important consideration in exploring the effects of ETS exposure is the biological plausibility of an effect. This issue is addressed by comparing findings from studies of ETS exposure to those of active smoking, and by examining the results of animal studies of exposure to tobacco smoke or chemical constituents of tobacco smoke, short term tests and biomarker investigations.

#### 1.3.1. Measures of Exposure in Epidemiological Studies

Characterization of ETS exposure in most epidemiological studies is limited to broad categories (*e.g.*, yes/no, number of hours per week). Accurate categorization is difficult, given the large variation in exposures individuals experience. Exposure has generally been determined in three ways: ascertainment of spousal smoking status; estimation of the number of hours a person is exposed (at home, at work, or elsewhere); or measurement of biomarkers. Interviews or questionnaires are often used to collect the first two types of information. Some of the limitations of assessing ETS exposure are briefly discussed below, while Part A (update of the

original Chapter 2) provides more detail on exposure measurement using biomarkers, and examines issues regarding the use of questionnaires.

Misclassification is an important consideration when reviewing epidemiologic studies. Misclassification of exposure status occurs when individuals are categorized as being more or less exposed than they actually were. If the likelihood of misclassification does not depend on whether the study subjects are diseased or not (that is, misclassification is "nondifferential"), then an association between ETS and the disease will be more difficult to detect. Misclassification is a concern in studies which rely on the ascertainment of spousal smoking status, because ETS exposures also occur outside the home. In addition, the amount smoked by the spouse outside and inside the home, as well as the time spent in the home by the nonsmoking spouse, varies from couple to couple. Other considerations include size and ventilation of the subjects' residences. Misclassification can occur when exposures observed at one point in time are assumed to apply to other time periods. This is a particular problem when there are windows of susceptibility at a particular lifestage but exposure information are missing for that important window. Misclassification can also be an issue when exposure is determined by asking subjects about the number of hours they are exposed, for example, at home or work. While questions on number of hours exposed provide more information about multiple exposure sources, respondents may vary in their awareness of and ability to quantify their exposure (Coultas *et al*., 1989). The tendency is toward underestimation of hours exposed (Emmons *et al*., 1992). Few studies of this type attempt to verify self-reported exposures.

Misclassification of exposure to passive smoking by limited exposure ascertainment results in referent groups which contain people who have been or are exposed to ETS. The misclassification of smokers as nonsmokers affects a very small percent of the nonsmoking referent group in the majority of studies (less than 5%). However, virtually all nonsmokers have been exposed at some point to ETS, particularly in the past when smoking was more prevalent and there were no restrictions on smoking in the workplace, at schools, or in public places. Thus, practically speaking, while a referent group may have a stray light smoker, almost 100% of the people in the referent group of all studies with poor ascertainment of exposure have had at least some exposure to ETS, and in many cases significant long-term exposures. Johnson notes in a letter published in JNCI (2001, 93:720) that Fontham et al. (1994) found that 64% of never-

smoking women in the U.S. reported social exposure and 60% reported exposure at work. The majority of these exposures occurred over many years. The implication is that the referent categories of non-exposed people can in fact be highly contaminated with exposed individuals if the study only assesses spousal smoking status. Even studies that do a more thorough assessment of all sources of ETS exposure are likely to have some individuals in the referent category with at least some ETS exposure. The result of such misclassification is to bias the results towards the null.

To minimize misclassification errors, the occurrence and duration of exposure to all sources of ETS should be ascertained as completely as possible. More recent studies have used measurement of biomarkers of exposure to improve assessment of ETS exposure. The biomarker cotinine, a metabolite of nicotine with relatively short half-life (20-30 hours in blood plasma), is useful in categorizing and verifying recent exposure. However, because it only reflects exposures of the past day or two, it is less useful in evaluating chronic exposure. Measurement of cotinine can also be useful for identifying active smokers, as levels generally differ between smokers and nonsmokers exposed to ETS by one to two orders of magnitude.

Characterization of ETS exposure in studies of developmental effects which manifest perinatally or in the first year of life can be particularly challenging. Because of the pronounced effects of maternal smoking during pregnancy on some of the outcomes of interest, studies that can distinguish pre- and postnatal ETS exposure from *in utero* exposure due to maternal active smoking are given more weight. Some studies have attempted to control for maternal active smoking during pregnancy through statistical analyses. However, as spousal smoking habits are correlated, it is difficult to control for the effect of only one partner's smoking. In addition, almost all women who smoke throughout pregnancy continue to smoke after their babies are born (Fingerhut *et al.*, 1990) and thus expose their children both to mainstream and sidestream tobacco smoke components prenatally and to ETS after birth.

Assessment of current ETS exposure of children is somewhat less problematic. Although concerns similar to those discussed above regarding misclassification remain, children, especially infants and young children, are likely to be exposed to tobacco smoke in fewer circumstances than adults. Cotinine concentrations in children are well correlated with smoking

by the mother (Greenberg *et al.*, 1989; U.S. DHHS, 1986); thus, information on cigarette consumption by the mother is likely to provide a reasonable proxy for a young child's ETS exposure. This may not be the case if the mother is not the primary caregiver. The use of paternal smoking alone as a proxy for ETS exposure of infants and children can be problematic, as fathers are generally less likely to be the primary caregiver.

### 1.3.2. ETS Exposure in Animal Studies

Two main exposure issues arise in examining animal studies of tobacco smoke effects. First, there are no direct analogues of active smoking in animals; in all cases the smoke is dispersed in the air rather than pulled from a cigarette into the lungs. Secondly, in many study reports not enough methodological detail is provided to determine whether the smoke generated can be classified as “mainstream” or “sidestream” smoke, and thus its relevance to ETS exposure is unclear. The majority of the studies available have attempted to simulate active smoking by using mainstream smoke, and some delivered the smoke in bursts or “puffs”. A few recent studies have used exposures characterized as “sidestream smoke,” which is considered more relevant to the assessment of the effects of ETS exposure than studies of only mainstream smoke. Of course a mixture of mainstream and sidestream smoke would be most relevant.

### 1.3.3. Measures of Effect

The association of ETS exposure and a specific outcome in an epidemiologic study is usually reported as an odds ratio or a rate ratio with a confidence interval, if available from reported studies. Odds and rate ratios adjusted for potential confounders in the original studies are included when available. An important consideration in examining causality is whether a dose-response effect was found, so when available those findings are included.

In general, in evaluating the findings of a study, the statistical significance of single comparisons, as indicated by the p-value, is considered. However, when evaluating a body of epidemiologic literature, basing interpretation only on the tallying of statistically significant findings can be misleading (Greenland, 1987; Frieman *et al*., 1978). One problem is that epidemiologic data seldom satisfy the criteria of randomized experimental trials, for which the statistical testing methods were designed. Furthermore, statistical significance is influenced by

sample size; not all studies may be large enough to detect a significant association of a given magnitude. This is especially the case if the effect is expected to be of relatively small magnitude, as is anticipated for several of the potential ETS endpoints. Finally, comparisons simply on the basis of p-values do not take into account possible sources of bias in the studies. Furthermore, there is a wealth of information from toxicity testing in animals of many constituents of ETS. Consideration of such animal toxicity data is routine practice in regulatory risk assessment, and provides important information on potential health effects in humans. Therefore, in evaluating causality for a particular endpoint, the overall body of evidence including information from toxicological testing of ETS constituents is carefully considered.

### 1.3.4. Attributable Risk

To provide a context for judging the importance of effects caused by ETS exposure, estimates of ETS-related morbidity and mortality are provided. The estimates are derived from data on prevalence and relative risk, through assessing the attributable fraction, also called the attributable risk (Breslow and Day, 1980; Kelsey *et al.*, 1996). The attributable fraction is the proportion of disease occurrence potentially eliminated if exposure was prevented. U.S. EPA (1992) used an attributable fraction approach in estimating national figures for ETS-related respiratory health effects. In fact, the national figures derived by U.S. EPA (1992) were used as part or all of the basis for deriving California-specific values for childhood asthma induction and exacerbation, bronchitis or pneumonia in young children, and lung cancer in the 1997 OEHHA document: the U.S. estimate was multiplied by 12%, the fraction of the U.S. population residing in the State. U.S. statistics reported in the published literature for ETS-related heart disease mortality (Wells, 1988 and 1994; Steenland, 1992; Glantz and Parmley, 1991) were similarly used to estimate California-specific impacts. In this report, we calculate California-specific values for specific endpoints, using California prevalence data for ETS exposure and appropriate relative risk values to first estimate the attributable fraction. In some cases, these values are lower in the new report as the prevalence of exposure has substantially decreased.

To the extent that smoking prevalence and ETS exposure have been declining in recent years attributable risk estimates may be slightly elevated, depending on the relative impacts of current versus past ETS exposures on the health endpoint. Cases of lung cancer occurring today are a

consequence of ETS exposures over past decades, and since smoking prevalence in California was near national levels until the mid-1980s, the differences noted in smoking prevalence should not significantly impact the accuracy of the California estimate. For heart disease mortality, this issue is more difficult to judge since the importance of current versus past exposures is not clearly understood. In addition, the population of both California and the U.S. has increased. Thus, more people are exposed even as smoking rates decline. Other sources of uncertainty in estimates based on the attributable fraction method include limited information on prevalence of current and past smokers and relative risks of disease associated with smoking status. Methods to describe the sensitivity of these factors to morbidity and mortality estimates derived using an attributable risk formulation have been published (Taylor and Tweedie, 1997).

### 1.4. Weight-of-Evidence Evaluations

A "weight-of-evidence" approach has been used to describe the body of evidence on whether or not ETS exposure causes a particular effect. Under this approach, the number and quality of epidemiological studies, as well as other sources of data on biological plausibility particularly in toxicology studies of ETS and ETS constituents, are considered in making a scientific judgment. Associations that are replicated in several studies of the same design or using different epidemiological approaches or considering different sources of exposure and in a number of geographical regions are more likely to represent a causal relationship than isolated observations from single studies (IARC, 1996). If there are inconsistent results among investigations, possible reasons are sought (such as adequacy of sample size or control group, methods used to assess ETS exposure, range in levels of exposure), and results of studies judged to be of high quality are given more weight than those of studies judged to be methodologically less sound. General considerations made in evaluating individual studies include study design, appropriateness of the study population, methods used to ascertain ETS exposure, as well as analytic methods, such as the ability to account for other variables that may potentially confound the ETS effect (see for example: IARC, 1996). Increased risk with increasing levels of exposure to ETS is considered to be a strong indication of causality, although absence of a graded response is not necessarily evidence against a causal relationship (IARC, 1996).

In judging the strength of associations between ETS exposure and health effects, criteria recommended by IARC, the Institute of Medicine (2004), and standard epidemiologic texts were considered. The early criteria for causality were initially developed for infectious diseases where there is one organism that can be seen to produce a disease (e.g., through Koch's postulates). For complex mixtures where many toxicologically active materials are present such as ETS, and where the health outcomes are complex diseases, such as cancer, the earlier criteria are still quite useful but may not be as practical simply due to the multi-factorial nature of complex diseases. Lilienfeld and Lilienfeld (1980) note "*In medicine and public health, it would appear reasonable to adopt a pragmatic concept of causality. A causal relationship would be recognized to exist whenever evidence indicates that the factors form part of the complex of circumstances that increases the probability of the occurrence of disease and that a diminution of one or more of these factors decreases the frequency of that disease. After all, the reason for determining the etiological factors of a disease is to apply this knowledge to prevent the disease.*" In this report, an effect is judged to be causally associated with ETS exposure when a positive relationship between ETS exposure and the effect has been observed in studies in which chance, bias and confounding could be ruled out with reasonable confidence. The evidence must satisfy several of the guidelines used to assess causality, such as: strength of association, biological plausibility, coherence, dose-response relationship, consistency of association, and temporal association. Effects considered to have suggestive evidence of a causal association with ETS exposure are those for which a causal interpretation can be considered to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence. For example, at least one high quality study reports a positive association that is sufficiently free of bias, including adequate control for confounding. Alternatively, several studies of lower quality show consistent positive associations and the results are probably not due to bias and confounding. For several effects, the evidence was judged to be inconclusive, since it was not possible to determine whether or not ETS exposure affects the severity or prevalence of their occurrence. Either too few studies are available to evaluate the impact, or the available studies are of insufficient quality, consistency or statistical power to permit a conclusion.

Unlike most environmental contaminants, ETS-related health impacts are directly observable through studies of people in exposure situations that are also experienced by the general

population. Still the relative risks observed can be small, requiring a number of studies or large studies to confirm the effect. Some endpoints have not been sufficiently studied epidemiologically, in which case the finding that the data are inconclusive based on inadequate evidence should be seen as preliminary. Because the epidemiologic data are extensive, they serve as the primary basis on which findings of ETS effects are made. Experimental animal data are reviewed to determine the extent to which they support or conflict with the human data. In some cases, studies of ETS constituents in experimental animals are used to support the weight-of-evidence judgment. As noted above, this is standard practice in risk assessment. In many instances in the Toxic Air Contaminants program, chemicals have been identified as TACs and emissions have been regulated based on animal toxicological data alone. This is important in the public health setting because oftentimes adequate epidemiological data do not exist.

It has been argued that the biological plausibility of a presumed health effect of ETS depends on it being observed (generally, to a greater extent) as a result of active smoking. This assumption may be problematic, especially where a particular biomarker is used as the index of exposure to tobacco smoke for both active and passive smokers. The concentrations of constituents in mainstream smoke and ETS differ (in some cases by > ten fold), so there may not be a constant ratio between a biomarker of exposure and the actual exposure to a toxicologically active component for both types of tobacco smoke exposure. In addition, the dose-response curves for specific toxic effects may be non-monotonic. Under appropriate circumstances, where the dose response shows saturation, the effect of exposures in the range characteristic of ETS could be nearly maximal, with any additional exposure during active smoking having little or no effect. Conversely, if certain types of toxic or pharmacological effect show a threshold, there might be a marked effect of active smoking but no effect of ETS exposure. In situations where the overall response to active components is a complex result of several different simultaneous effects, this could even produce qualitatively different responses to ETS and active smoking.

**Table 1.1 Attributable Risks Associated with ETS**

| | **Conclusion OEHHA 1997** | **Conclusion OEHHA 1997** | **Conclusion Update** | **Conclusion Update** |
|---|---|---|---|---|
| Outcome | Excess # in CA | Excess # in US | Excess # in CA | Excess # in US |
| Pregnancy:<br>Low Birth Weight<br>Pre-Term Delivery | 1,200-2,200 | 9,700-18,600 | 1,600<br>4,700 | 24,300[1]<br>71,900 |
| Cardiac death (Ischemic heart disease death) | 4,200-7,440 | 35,000-62,000 | 1,700-5,500[2] | 22,700-69,600[3] |
| Lung Cancer Death | 360 | 3000 | 400[4] | 3400 |
| Asthma (children):<br>Episodes<br>New cases<br>Exacerbation | | | | |
| | | | 31,000 [5] | 202,300 [6] |
| | 960-3120 | 8,000-26,000 | | |
| | 48,000-120,000 | 400,000-1,000,000 | | |
| Lower respiratory illness | 18,000-36,000 | 150,000-300,000 | N/A | N/A |
| Otitis media visits | 78,600-188,700 | 700,000-1,600,000 | 51,700 [7] | 789,700[8] |
| SIDS | 120 | 1,900-2,700 | 21 [9] | 431[10] |
| Breast cancer | | | All studies: OR 1.26 (95% CI 1.10-1.45)[11]<br>Best studies: OR 1.90 (95% CI 1.53-2.37)<br>Approximate 26 - 90% increased risk | |

1 Based on adult females reporting exposure to ETS in NHANES III for 1995 (Pirkle et al., 1996)

2 Based on California Dept Health Services. www.dhs.cs.gov/hisp/chs/OHIR/vssdata/2000data/OOCh5pdf/5_9_Reorg.PDF. Table 5-9 for yr 2000

3 Based on Anderson and Arias (2003). National Vital Statistics Report. Vol 51(9) Table 2 for yr 2000 Ischemic heart diseases including AMI.

4 Assuming California exposure and death rates are similar to national rates and California population is 12% of national population.

5 Based on number asthma attacks or episodes in previous 12 months for 0-17 year olds. Calculated from California Health Interview Survey for 2001

6 Based on number asthma attacks or episodes in previous 12 months for 0-14 year olds. CDC-MMWR 2002 51(SS01)

7 Calculated by applying national value (H6) and assuming 12% of US population lives in California

8 Based on National Center for Health Statistics Series 13 No. 137. Ambulatory Health Care Visits by Children: Principal Diagnosis and Place of Visit for yrs 1993-1995.

9 Based on California Dept Health Services. www.dhs.ca.gov/hisp/chs/ohir/vssdata/2000data/00ch4pdf/8reorg.pdf. Table 4-8 for yr 2000

10 Based on National Center for Health Statistics. www.cdc.gov/nchs/fastats/infort.htm for yr 2000
LBW = low birth weight; N/A = data not available.

11 OEHHA is unable at this time to calculate an attributable risk as it is not possible to account accurately for the portion attributable to other known risk factors. The OR for all studies is based on our meta-analysis of all studies overall risk estimates. The OR for best studies is based on the OR for all studies which did a better job of ascertaining exposure – see Section 7.4.1.3.2 and Table 7.4.1l.

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